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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/653,924	09/01/2000	David A. Horwitz	A-67689-3/RFT/RMS/RMK	7255

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	16

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/653,924	HORWITZ, DAVID A.	
	Examin r	Art Unit	
	Maher M. Haddad	1644	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-8,10,14-17,29-36 and 38-42* is/are pending in the application.

4a) Of the above claim(s) *5,7,8,14,16,17,34-36 and 38-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 6, 10, 15, 29-33 and 41-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/10/03 (Paper No. 15), is acknowledged.

2. Claims 2,5-8,10,14-17,29-36 and 38-42 are pending.

3. Claims 5, 7-8, 14, 16-17, 34-36 and 38-40 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 2, 6, 10, 15, 29-33 and 41-42 are under consideration in the instant application a method for treating donor cells to ameliorate grafte versus host disease in recipient patient, comprising PBMC enriched for CD3+CD4-CD8-, treating said cells with TGF-β or a TGFβ and IL-2 and the T cell activator is anti-CD3.

5. The following new grounds of rejections are necessitated by the amendment filed on 3/10/03 (Paper No. 15).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 2, 6, 10, 15, 29-32 and 38-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "IL-2 and a T cell activator" is indefinite because IL-2 is a T cell activator and it is unclear whether the T cell activator reads on IL-2 or other T cell activators.

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 2, 6, 10, 15 and 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-4 of U.S. Patent No. 6,447,765 in view of U.S. Patent No. 6,406,696.

Claims 1 and 3-4 of U.S. Patent No. 6,447,765 teach a method of treating a donor cells to ameliorate graft versus host disease in a recipient patient comprising (a) removing peripheral blood mononuclear cells (PBMC) from a donor; (b) treating said cells with a suppressive composition comprising TGF-β for a time sufficient to induce T cell tolerance; and (c) administering said cells to said patient in patented claim 1, wherein said suppressive composition further comprises IL-2 in patented claim 4, and the method further comprises adding said cells to donor stem cells prior to administering to said patient in patented claim 3.

The claimed invention differs from the reference claims 1and 3-4 recitations only by the recitation the suppressive-inducing composition comprising TGF-b, IL-2 and a T cell activator, wherein the T cell activator is anti-CD3 in claim 33.

The `696 patent teaches immunopotentiating agents include monoclonal antibodies, such as anti-CD3 which activate T cells (see abstract in particular). Moreover, the `696 patent teaches the ability of anti-CD3 to abrogate graft versus host disease (GVHD) in a murine model wherein the anti-CD3 mAb treatment also enhanced bone marrow engraftment (column 12, lines 42-46 in particular) and the circulating anti-CD3 antibody would modulate TcR from host T cells and thereby inhibit HVD reactions (column 18, lines 50-54 in particular). Furthermore, monoclonal antibodies (mAb) to T lymphocyte antigens have been used to suppress immune responses in vivo and in vitro by blocking T cell receptor-mediated antigen recognition, a property exploited clinically to prevent and reverse organ transplant rejection (column 14, lines 62-65 in particular).

Claims 10 and 15 are included because both the reference teachings and the claimed invention involved the same method of treating donor cells to ameliorate graft versus host disease in a recipient patient which comprises administration of same product to the same recipient patient.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to further activate the recipient T cells with anti-CD3 antibody taught by the `696 patent in the method of treating donor cells to a meliorate graft versus host disease taught by the `765 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such immunopotentiating antibodies suppress immune responses in vivo and in vitro by blocking T cell receptor-mediated antigen recognition, a property exploited clinically to prevent and reverse organ transplant rejection as taught by the `696 patent.

Applicant's arguments, filed 3/10/02 (Paper No. 14), have been fully considered, but have not been found convincing.

Applicant argues that the `765 patent discloses a method for treating donor cells to ameliorate graft versus host disease comprising treating donor PBMC with a suppressive composition comprising TGF-β and the dependent claim 4 recites that the suppressive composition further comprises IL-2. Applicant asserts that claims 1 and 3-4 of the `795 patent do not teach a suppressive composition comprising a T cell activator.

Contrary to applicant assertions the instant specification on page 17, lines 8-12, defined the T cell activator to include anti-CD3, anti-CD28, anti-CD2, IL-2, IL4, IL-15 and mitogens such as Con A and SEB, wherein patented claim 4 of the `765 patent recites the suppressive composition further comprises the T cell activator IL-2. Similarly, the `765 patent specification, column 13 under Example 5, discloses different T cell activators such as Con A, SEB, IL-2, or IL-10 in combination with TGF-β.

Applicant argues that the claims of `696 patent do not teach or disclose a method for using a suppressive composition comprising TGFβ, IL-2 and a T cell activator to ameliorate graft versus host disease. Applicant asserts that the obviousness-type double patenting rejection is analogous to the obviousness rejection based on 35 U.S.C. §103, except that only the claims in the cited patents or applications are considered prior art.

However, A double patenting rejection of the obviousness-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. In re Braithwaite, 379 F.2d 594, 154 USPQ 29 (CCPA 1967). Therefore, any analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. In re Braat, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). See MPEP 804.

The `765 patent was used as the patent principally underlying the double patenting rejection, wherein claims are considered prior art, however, the `696 patent was used as to show the obviousness type rejection, wherein the teachings of the patent are applied.

Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven,* 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

10. Claims 29-33 and 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3-4 of U.S. Patent No. 6,447,765 in view of Sykes *et al* (Cell Immunol. 129(2):478-493, 1990) and further in view of U.S. Patent No. 6,406,696.

Claims 1, 3-4 of the ''765 patent and the teachings of `696 patent have been discussed, supra.

The claimed invention differs from the reference claims 1, 3-4 recitations only by the recitation that PBMC are enriched for CD3+CD4-CD8- cells.

Sykes *et al* teach that enriching and then propagating natural suppressor cells derived from T cell-depleted cells *in vitro* can enhance anti-GVHD effect by adoptive transfer in vivo. Using IL-2 to produce two cell lines of BMC depleted of Mac1-positive cells and of Mac1-positive plus Thy1-positive cells, these cells express CD3 but not CD4 or CD8 (page 490, under Discussion in particular). These cell lines demonstrated suppressive activity in vitro, cytolytic activity against a broad range of natural killer (NK)-sensitive and NK-resistant targets, and a novel cell surface phenotype, with characteristics of both alpha beta-TcR-bearing T cells and of NK cells.
Sykes *et al* further teach that natural suppressor (NS) cells derived from T cell-depleted (TCD) syngeneic marrow can protect against GVHD while permitting alloengraftment (see abstract and page 478 in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to enrich PBMC for CD+CD4-CD8- cells taught by Sykes *et al* reference and further activate the recipient T cells with anti-CD3 antibody as taught by the `696 patent in the method of treating donor cells to a meliorate graft versus host disease taught by the `765 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such enriched cells can be protective against GVHD while permitting alloengraftment as taught by Sykes *et al* and further, such immunopotentiating antibodies suppress immune responses in vivo and in vitro by blocking T cell receptor-mediated antigen recognition, a property exploited clinically to prevent and reverse organ transplant rejection as taught by the `696 patent.
Applicant's arguments, filed 3/10/02 (Paper No. 14), have been fully considered, but have not been found convincing.

Applicant argues that Sykes et al do not teach selectively CD+3CD4-CD8- subset from donor PBMC and then treating that subset with a suppressive composition comprising TGFβ, IL-2 and a T cell activator.

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

11. No claim allowed

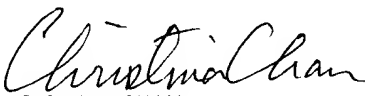
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
May 1, 2003



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